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H. W. WILEY, Chief of Bureau.

ADULTERATED DRUGS AND CHEMICALS.

I. Inferior Drugs and Insidious Methods of Deception.
II. Rose Geranium Oil and Its Substitutes.
III. Phenacetin: Methods of Analysis and Commercial Status.

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LETTER OF TRANSMITTAL.

U. S. Department of Agriculture,
Bureau of Chemistry,
Washington, D. C., November 6, 1903.

Sir: I have the honor to transmit for your inspection and approval a manuscript reporting the results of investigations relative to the adulteration of certain drugs and chemicals. These investigations were carried on chiefly in the drug laboratory of this Bureau, although some of the work described was done by Mr. Kebler before taking charge of that laboratory. I recommend that this manuscript be published as Bulletin No. 80 of this Bureau.

Respectfully,

H. W. Wiley, *Chief.*

Hon. James Wilson,
Secretary of Agriculture.

INTRODUCTION.

The first two articles of this bulletin set forth the conditions that prevail not only in relation to individuals, but also in some of the best-regulated laboratories. There is a continual cry for cheaper drugs, and in the effort to meet this demand and at the same time make a profit adulteration has spread. The members of the pharmaceutical profession of high standing, however, are anxious to remove from the trade any odium due to adulteration which at present exists.

The third paper deals with the patented medicinal remedy phenacetin, which according to reports has been largely adulterated in this country and many substitutes offered therefor. This subject was studied because of the great interest that exists concerning it in both the medical and the pharmaceutical world, many druggists and physicians being directly involved in the controversy. The fact that phenacetin is sold for 15 cents an ounce in Canada, while $1 or more is charged for the same amount in the United States, creates an impression, correct or incorrect, of injustice. The conditions set forth concerning phenacetin are, moreover, typical of those affecting a large number of patented medicinal remedies. Furthermore, the attempts that have been made to secure such changes in the patent laws as would eliminate these disturbing factors have not been successful. It is hoped that the contents of this paper will place the whole situation before the public in a just and impartial manner.

H. W. WILEY,
Chief of Bureau.

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ADULTERATED DRUGS AND CHEMICALS.

I.—INFERIOR DRUGS AND INSIDIOUS METHODS OF DECEPTION.

INTRODUCTION.

The adulteration of medicinal remedies is brought to our attention from time to time, and it will probably not be denied by many that the basic facts as given to the public are, in the main, correct; but frequently the worst possible interpretation is given them. There are, undoubtedly, members of the pharmaceutical profession whose sense of honor is so distorted by rapacity and greed that they unconsciously, if not deliberately, drift into mendaciousness. These are the men who usually bring the craft into ill repute. Some of the excuses given by these dealers, when informed concerning the shortcomings of their goods, are both interesting and instructive. For example, they contend that it would not be safe to supply their customers with laudanum of full pharmacopœial strength, having in former days used a weaker preparation. Then again, some articles must be modified to suit the tastes of the public, for example, by imparting a certain color to a given preparation. Most of these excuses must be taken *cum grano salis*, but there are undoubtedly adulterations of long standing, such as "limed nutmegs," "bleached ginger," etc., that should be leniently dealt with at present, for it is well known that according to certain ancient methods of curing still practiced the kernels of nutmegs and the rhizomes of ginger are treated with lime to ward off the ravages of insects. Every possible effort should be made to have goods of this character labeled so as not to mislead the consumer. The great difficulty in making any concession whatever is that it might be construed as excusing the dealer's actions and thus embolden him in his insidious sophistry.

When the physician is called to guide a patient through an illness his therapeutic knowledge is generally called into play, and he prescribes for the sufferer on the basis of pure drugs. If he is deceived in the quality of the agents delivered and administered, abnormal symptoms may arise for which the doctor is unable to account, and consequently he is placed in a very embarrassing position. As can readily be seen, most disastrous results may ensue, for which the

apothecary is responsible. Many a physician realizes the gravity of the situation, and in self-defense and for the welfare of his patients he prescribes certain brands of recognized purity or carries and prescribes his own remedies, made for him by reputable firms, rather than trust the local druggist with the filling of his prescriptions.

The joint committee of the American Medical Association and the American Pharmaceutical Association, appointed to consider the feasibility of establishing a national bureau of medicines and foods, in its report to the latter body recommended the adoption of the following preamble and resolutions:

Whereas the foods and medicines supplied in the United States do not so uniformly agree with proper standards of purity, quality, and strength as they should; and

Whereas a degree of distrust and want of confidence concerning the quality of such foods and medicines prevails to a discouraging extent: Therefore it is

Resolved, That a more perfectly organized system for remedying the above-mentioned conditions than that now existing should be devised and put into operation; and

Resolved, That the American Pharmaceutical Association and the American Medical Association, acting in harmony with the United States Government authorities, constitute the most competent and trustworthy means for obtaining the object named.

Only two of the resolutions are quoted, but they serve to show in a concise manner the present condition of affairs.

During recent years Federal and State authorities have enacted laws which if properly amplified and conscientiously and intelligently enforced will in due time minimize the adulteration of medicinal agents and improve the quality of chemicals. These statutes generally recognize that there are numerous methods by which the quality of a commodity may be impaired. The object of this paper is to discuss some of these methods, cite examples taken from actual practice, and call the attention of the pharmaceutical and chemical world to the various forms of adulteration, which may be subdivided as follows: (1) Conventional, to suit the tastes and demands of the public; (2) accidental or incidental, arising from environment, carelessness, or incompetence on the part of the producer or manufacturer or his agents; (3) arbitrary, to comply with or take advantage of certain fixed, arbitrary standards; and (4) intentional, for gainful purposes and competition.

CONVENTIONAL ADULTERATIONS.

Conventional adulterations, such as silvered cochineal, bleached ginger, and the artificial coloring of many products, have been brought about in various ways. The original object in many cases undoubtedly was to trade on the credulity of the public, for it is a well-known fact that an attractive physical appearance is a great factor in the sale of goods, and color usually carries with it an idea of strength and quality. Such a firm footing have these factors secured that in some cases the adulterated article is selected rather than the pure. To illustrate, a

few years ago, while exhibiting a sample each of pure and weighted cochineal, a recent graduate of one of our well-known colleges, after looking them over thoroughly, selected the adulterated article as the genuine product. When informed of his error, somewhat chagrined at his mistake, he said, "It is the only kind I have ever seen and of course I thought it was the pure article." From this and similar experiences it would seem that some of our educational institutions are not exercising as much care as they might in the selection of their material for instruction purposes.

The artificial coloring of preparations is the most widespread of conventional adulterations. These pages will probably not come under the eyes of a single reader who is unable to enumerate a score of such products. To suggest a multitude of these goods it is only necessary to enumerate elixirs, tinctures, sirups, essences, pills, and tablets. As long as the harmless vegetable colors were used little cause for anxiety existed, but of late the danger line has been passed by the extensive use of aniline dyes. The finding of harmful coloring agents in food products is a matter of common repute, and medicines are not exempt. It would probably not be desirable to interdict the use of harmless coloring agents, but their use should be discouraged. In cases where it is clearly evident that fraud is concealed by coloring agents, as in the preparation of vanilla extract from the chemical vanillin, dissolved in a suitable menstruum and colored with caramel, a suitable punishment should be provided.

It is quite possible that an attractively colored preparation is more palatable than one that is not colored, but the nature of the coloring agent should, in such case, be plainly set forth on the label, unless it is part of a formula contained in some recognized authority like the Pharmacopœia or the National Formulary.

BLEACHED GINGER.

The bleaching of ginger by covering the fingers with some white substance, like calcium carbonate, is frequently done to cater to the fancy of certain customers. It also seems to be incidental to certain processes of curing. In some cases, however, the prime motive is to conceal inferiority. The amount of coating added usually does not exceed 5 per cent, but the increase in price is about 15 per cent. In bleaching ginger considerable care must be exercised in the selection of the fingers, or the shrinkage due to loss of moisture will be equal to the amount of weighting material added. At all events the purchaser of bleached ginger pays more money and gets less ginger than if he purchased the unbleached variety.

COCHINEAL.

Availability of the Pure Product.

It seems that the cochineal industry is grossly involved in adulteration, and, according to some dealers, irretrievably lost to this practice. They contend that it is almost impossible to purchase a pure article on the open market, but an investigation shows that this contention is not well founded. In fact, the pure product is so easily secured that adulterated cochineal would be placed under the fraudulent form of adulteration if it were not well known that the consumer virtually knows only the silvered or commonly adulterated variety. The object of the work done on cochineal was to ascertain, not the extent of the adulteration, but how difficult it is to obtain the pure article. It was soon found that pure cochineal was readily available when demanded. A number of samples examined gave the following results:

Analyses of cochineal.

Serial No.	Source.	Kind.	Ash.	Adulterant.	Moisture at 105° C.	Coloring matter.		Price per pound.
						Colorimetric.	1 per cent solution of K_3FeCy_6.	
			Per ct.		*Per ct.*		*cc.*	
3	.....	Silver	30.81	Talcum	6.7	64	1.2	$0.40
156	Eimer & Amend	Powdered	17.25	Earthy matter.	6.25	50	1.0	.45
157	Smith, Kline & French Co.	Black	4.94	None	7.00	100	1.8	.45
158	do	Powdered	6.06	do	6.15	100	2.0	.50
159	do	Silver	3.01	do	6.38	92	1.3	.40
165	Eimer & Amend	Black	4.71	do	7.73	100	1.9	.....

Nos. 3 and 156 represent goods delivered to the Bureau of Chemistry without specification. No. 159 was sent with the belief that it was adulterated. Nos. 157, 158, and 165 were delivered as pure goods, and an examination proved such to be the case. On account of the high price, the variable quality, and the customary adulteration of cochineal, suitable methods for readily determining its quality are very desirable.

Methods of Analysis.

The per cent of ash is a fair index in determining the purity of cochineal, but this factor can easily be circumvented by the addition of starch, mixing exhausted material with the pure article, or molding paste into small grains to resemble closely the outlines of the insects themselves. The ash of normal cochineal should never exceed 6 per cent.

The most reliable procedure to determine the quality of cochineal is to estimate the amount of carmine either colorimetrically or by one of the oxidation methods. J. Löwenthal's[a] well-known method for

[a] Ztsch. anal. Chem., 1877, **16**: 179.

the determination of tannin can be employed to advantage only when considerable work of this character is done. F. Penny's[a] process appears to have many advocates. The basis of this method is the oxidation of the coloring material in an alkaline solution by means of a 1 per cent solution of potassium ferricyanid. It is executed by digesting together, on a water bath, for one hour, 1 gram of powdered cochineal and 5 grams of caustic potash, dissolved in 20 cc of distilled water. Avoid dissipation of the water, dilute the resulting mixture to 100 cc. and titrate an aliquot part by means of the potassium ferricyanid solution. The carmine red color is changed to a brownish yellow. The transition of color is indistinct and the exact end reaction is difficult to determine. In this work 20 cc of cochineal solution were used for each titration.

Except in cases where cochineal is to be used for special purposes, a simple colorimetric method gives satisfactory results. For this purpose the following process is suggested:

Digest on the water bath for one hour, 1 gram of powdered cochineal and 1 gram of potassium hydroxid, dissolved in 20 cc of water; replenish the water as it evaporates and make the mixture up to 100 cc with distilled water. Dilute 10 cc of this solution to 400 cc. The color thus obtained, from a cochineal of known purity, is taken as the basis and called 100. If pure cochineal always possessed the same tinctorial value and were a well-known commercial article, the color obtained by the above procedure could be utilized as a standard. A readily available uniform standard is, however, found in a properly diluted aqueous solution of potassium permanganate. It has been found that by diluting 12.5 cc of a centinormal potassium permanganate solution (0.316 gram of pure potassium permanganate dissolved in 1 liter of distilled water) to 100 cc, a tint of color is obtained, when observed in a Nessler tube held at a right angle to the eye of the worker, which is identical to that prepared from pure cochineal by the process described above. By adopting this potassium permanganate solution as a standard, and calling it 100, the tinctorial value of every sample of cochineal can be ascertained and definitely expressed. If a sample of cochineal should be found in the future possessing a higher coloring equivalent than any met in this work, the standard of comparison would not need to be changed, but could be expressed by 110, 125, etc., as the case may be.

According to the above method, Nos. 157, 158, and 165 are of good and equal quality, No. 159 is of fair quality, and Nos. 3 and 156 are decidedly inferior, having only about one-half and two-thirds, respectively, the coloring value of a normal cochineal. A microscopic examination of No. 159 indicates that the silvering is due to rod-shaped bodies, like bacilli, but the usual bacterial stains would not effect them. It

[a] Rept. Brit. Assoc. Advanc. Science, 1855, pt. 2, p. 68.

is quite possible that the whitish appearance is due to a dried residue of cryptogamic plant growth. It is interesting to note that the results obtained by the potassium ferricyanid process run nearly parallel with the colorimetric data.

The physical appearance of these conventionally adulterated articles has secured such a firm footing in the public mind that it is almost impossible to replace them by pure goods. To eradicate these deeply inculcated erroneous ideas will require years of patient effort by way of both exposure and education.

ACCIDENTAL ADULTERATIONS.

Accidental adulterations are very widespread, and it is frequently difficult to say where this form of adulteration ends and the fraudulent begins. Crude drugs usually contain admixtures of twigs, stems, dirt, foreign leaves, and a host of other bodies. The Pharmacopœia does not make any allowance for contaminations of this kind, but dealers contend that such hypothetical requirements are purely academical and have no place in the commercial world. The argument is also advanced that certain drugs are collected by ignorant, semi-civilized people who can not be expected to eliminate impurities of this character. Excuses of this nature do not in any way relieve dealers and manufacturers from their responsibilities to the public. It is plainly their duty to handle and use only goods of the proper quality. To what extent some of these foreign articles modify the primary action of a drug can not be conjectured.

A certain few of the large drug houses of this country are eliminating these impurities by garbling. When it is remembered that the foreign material frequently amounts to 20 per cent or more it is quite evident that the cost of garbled goods is materially increased and that dealers in clean drugs are distinctly handicapped when brought into competition with those who handle inferior grades. It would probably be unjust to request a complete absence of foreign material, but a maximum limit could readily be fixed. A concerted effort should be made by all large manufacturers to establish a uniform high standard for all drugs used by them either in the making of finished medicinal remedies or for powdering. All purchases should be made on the basis of an adopted standard, paying only for the actual amount of good material in a consignment.

By a recent act of Congress the Secretary of Agriculture is authorized to investigate the quality of drugs imported into this country. The drug laboratory has already taken steps toward the securing of samples, which will be carefully investigated, in cooperation with the Bureau of Plant Industry.

It would probably be too exacting to require a root to be freed from all extraneous matter, but an upper limit of ash should certainly be

fixed. Some time ago a sample of golden seal root was received which was intended for powdering; it contained 23.8 per cent of ash and 2.02 per cent of hydrastine alkaloid, based on the air-dried material. A normal root should not contain more than 10 per cent of ash and not less than 2.5 per cent of hydrastine alkaloid. With golden seal at 60 cents per pound this dirt is a profitable addition for someone.

Certain leaves almost always contain a considerable amount of foreign matter. Chimaphilla leaves have been seen which were mixed with 25 per cent of stems. A sample of jaborandi leaves recently examined contained not less than 16 per cent of twigs and stems. A coca leaf sample on assay indicated 0.52 per cent of cocaine alkaloid, but the leaf was mixed with at least 18 per cent of foreign material. No valid excuse exists for this evil. Coca leaves containing as little as 3 per cent of foreign matter are readily available. A sample of cubeb berries on examination gave the following results: Stems, 15 per cent; worthless berries, 11 per cent; oil, 6.38 per cent. The physical appearance of the oil was good, its specific gravity 0.9384, and optical rotation −34.6°. The gravity is a little high but can hardly be considered abnormal. Good berries should yield not less than 12 per cent of oil.

DETERIORATED DRUGS.

The sample of cubeb berries referred to serves as an excellent example of transition between drugs containing foreign admixtures and those that have deteriorated by age or manner of keeping. To what extent these cheap, inferior, and in some cases worthless goods are used it is difficult to ascertain, but from information vouchsafed by brokers, drug millers, and manufacturers, this practice obtains to a considerable extent all about us. Deteriorations are incidental to the drug business, but the use of such goods, knowingly, in the manner indicated, is fraudulent, and what makes this practice so extremely reprehensible is the fact that it is very difficult, if not impossible, to detect inferior material of this character when powdered with goods of prime quality.

Articles particularly susceptible to change due to time are those containing essential oils, such as cinnamon bark, clove buds, lavender flowers, peppermint herb, sandal-wood chips, etc. A hundred-pound package of cinnamon-bark chips when submitted to distillation yielded only enough oil to impart a distinct flavor of cinnamon to 5 gallons of the aqueous distillate. Potent drugs with only a trace of alkaloids, due to old age, improper collection, or damage in transportation, are frequently used. Old jaborandi leaves deficient in alkaloidal strength are met with at times. Belladonna leaves improperly collected are not uncommon, and damaged coca leaves are occasionally placed on the market.

"C. P." CHEMICALS.

No less an authority than E. W. Morley during an interview said: "It is virtually impossible to make a chemical absolutely 100 per cent pure." From this it would seem that we must expect to find a small amount of foreign material in all chemicals. Experience shows such to be the case. These impurities are usually incidental to the process of manufacture, but when the amounts are excessive it must be ascribed to either carelessness, ignorance, or a desire on the part of the manufacturer to prepare a cheaper article at the expense of purity.

Chemical reagents are usually supplied as being chemically pure, "C. P." This designation was formerly supposed to mean, as it now should, a chemical of a high degree of purity. Whether this quality of chemicals was ever of a higher degree of purity than at present is difficult to ascertain. Occasionally we find a note in chemical literature to the effect that certain chemicals represented as free from impurities contained appreciable quantities of foreign matter. For example, Classen calls attention to two samples of "chemically pure" bismuth, sold for "scientific purposes," one of which contained 2 per cent of lead and the other 1.5 per cent of copper and 0.5 per cent of iron. Every sample of bismuth ever examined by the writer contained traces of arsenic and iron. Notwithstanding the fact that great improvements have been made in the manufacture of chemicals within recent years, the stage has not yet been reached in which chemicals are absolutely free from all impurities. It is true some of them will indicate a purity of 100 per cent, but this is usually due to the impurities in one chemical offsetting those in another, or to limitations of analytical methods. For example, recently a purchase of high-grade potassium permanganate was tested and found to analyze 100 per cent pure, and yet the chemical contained traces of nitrates and chlorids. The oxalic acid solution was prepared from oxalic acid that had been recrystallized in the laboratory with every possible precaution, and a careful examination showed that it was free from all impurities ascertainable by chemical analysis. Furthermore, the normal solution of oxalic acid was tested as to strength by the best methods and found to be correct.

The designation "C. P." as used at present is not only meaningless and worthless, but misleading in the extreme. Chemicals of the poorest character are marked "C. P." Manufacturers use the term carelessly, and dealers will attach it to any article of a chemical nature that they think will thus be made more attractive. Such dealings are an imposition on the consumer and unfair to honest competitors. Some time ago an examination was made of sodium carbonate crystals, C. P., delivered on a competitive bid, which were found to be about equal in quality to commercial English sal soda. Circumstantial evi-

dence pointed strongly to the conclusion that this dealer had simply marked the English brand with the classical abbreviation "C. P." and delivered it as such. Again, the writer has known of carloads of C. P. glycerin, shipped in iron drums, that contained a sediment consisting of iron scales, fibrous material, and other débris. These goods were also delivered on contract, awarded on sample submitted and competitive bid. If these consignments had not been examined on delivery they would have been accepted without question, but after their true nature became known they were promptly rejected. Honest dealers handling goods of prime quality can not successfully compete with articles of this character unless each consignment is examined.

A few more cases will be sufficient to show the quality of some of the C. P. chemicals frequently delivered. C. P. glycerin often contains arsenic and certain bodies that reduce an alkaline copper solution, and invariably contains volatile fatty acids. One sample of potassium iodid, C. P., was found to be contaminated with sulphates, iodates, and sodium compounds. It also contained 1.5 per cent of chlorid, and 5 grams required 3 cc of decinormal acid to neutralize the alkalinity. A sample of potassium bisulphate C. P. contained only 33 per cent of the acid sulphate. Some calcium oxid C. P. was found to contain iron, aluminum, magnesium, sulphate, and siliceous matter, being virtually no better than ordinary commercial quicklime. A sample of calcium chlorid C. P. was found to be contaminated with iron, aluminum, and magnesium, and was highly alkaline to litmus paper. Such articles would certainly be objectionable for analytical work.

Certain dealers, laboring under the delusion of hypercritical standards, have sought shelter behind the very elastic term "pure" and are supplying the market with chemicals which they think are sufficiently pure for all practical purposes. The term "pure" conveys distinctly different meanings to the artisan, assayer, broker, chemist, manufacturer, photographer, physician, and toxicologist. As a rule, these consumers do not call for chemicals free from all conceivable impurities, but demand the absence of certain specified contaminations which are detrimental in special work. The toxicologist must have his zinc free from arsenic, phosphorus, antimony, and sulphur, while traces of copper, carbon, or lead may not be objectionable.

There are a number of other terms used which at present convey very little information; they are Purum, Purissimum, Purified, Twice Purified, and Absolutely Chemically Pure; and even U. S. P., Br. P., and Ph. Ger. IV, are indifferently employed. Within recent years manufacturers have adopted a custom of marking some of their chemically pure chemicals "Free from manganese," "Free from sulphur," "Free from iron," "Arsenic free," "Free from silver,"

and "Strictly chemically pure, free from N. and S." The marking of chemicals as free from certain impurities is certainly a step in the right direction, but the great difficulty is that many of these chemicals are free from these impurities only on the label. A recent consignment of copper sulphate to be used in sugar analysis, delivered to the Bureau of Chemistry on the specification that it must be strictly free from iron, was so labeled, but nevertheless contained this impurity in appreciable quantities. A purchase of magnesium oxid guaranteed to be free from sulphur and so labeled contained over 2 per cent of sulphur calculated as anhydrous sodium sulphate, and goods labeled "Chemically pure sulphuric acid, arsenic free," frequently contain this impurity.

In view of the above facts it is quite evident, first, that "C. P," or "Chemically pure," with all its qualifying adjectives, at present means nothing, and its fraudulent use should be prohibited; second, that no chemical should be accepted as free from a certain impurity simply because the package is so labeled; and, third, that certain specific standards for chemical reagents should be established. Such reagents should be free from all undesirable or detrimental contaminations, and this fact should be set forth on the label. It is well known that many original packages are not marked at all except by the private mark of the manufacturer. A Federal law requiring that every package of chemicals be properly labeled as to name and quality would remedy this practice. V. Coblentz, in this connection, well says: "The indiscriminate labeling of chemicals without qualification as to degree of purity should by all means be discouraged as being a loose practice through which legal responsibilities may be evaded."

ADULTERATIONS RESULTING FROM ARBITRARY STANDARDS.

The argument is occasionally advanced that arbitrary standards are direct incentives to fraudulent dealings. Fluid extract of nux vomica prepared from a bean containing 2.5 per cent of total alkaloids is diluted, to conform to a standard, so that it contains only 1.5 per cent of alkaloids. Milk dealers reduce milk containing 5 per cent of fat, so as to pass a 3 per cent standard. The former is considered right, the latter reprehensible to a high degree. In reality the one does not appear to be any worse than the other.

The United States Pharmacopœia prescribes an upper and a lower limit of morphine for powdered opium, but no provisions are made to reduce an opium containing more than 15 per cent of morphine, the highest amount permissible, so as to conform to the proper requirements. It is not uncommon to meet with powdered opium containing over 15 per cent of morphine, and dealers are compelled in self-defense to reduce it to the proper strength by mixing it with opium of a lower

grade, or to use it in the manufacture of other medicinal remedies containing morphine. If the manufacturer places powdered opium on the market containing more than 15 per cent of morphine, he becomes liable to punishment, and if he dilutes it to the proper strength with a detectable diluent many State laws consider him culpable. In fixing standards of the above type it is desirable to provide for contingencies of this character.

Some dealers maintain that the pharmacopœial requirements of certain oils are abnormal and that adulteration must be resorted to if oils of the desired quality are supplied. Much capital is made of this in certain quarters, by quoting such oils as bay, coriander, and pimento, "compounded to conform to the requirements of U. S. P. 1890," at from 30 to 60 per cent below the price asked for pure oils which are not expected to comply with the pharmacopœial standards.

ANALYSES OF CERTAIN OILS AND POTASSIUM CYANIDS.

The most important factor in judging the quality of oil of bay, aside from its peculiar odor, is the specific gravity, which should lie, according to the Pharmacopœia, between 0.975 and 0.990, at 15° C. An examination of ten samples of pure oil of bay, obtained directly from the distillers, gave specific gravities varying from 0.958 to 0.980. All but two fell below the lower limit. Other recognized authorities allow a lower limit of 0.965. Three of the above samples fell below this standard, being 0.958, 0.9627, and 0.964, respectively. On submitting 511 pounds of bay leaves to steam distillation, 12.5 pounds of light and heavy oils mixed were obtained, which after aging one year had a specific gravity of 0.955. It would therefore seem that the specific gravity of the Pharmacopœia for oil of bay is a little too high.

Six samples of coriander-seed oil were examined, of which three were marked pure, two were distilled by the writer, and all complied with the U. S. P. requirements. The sixth was marked "German," and proved to be adulterated. The pharmacopœial standard is therefore not far from the truth.

Six samples of oil of pimento berries were tested. Their specific gravities were as follows: 1.0494, 1.0510, 1.0280, 1.034, 1.040, and 1.035. In other respects these oils complied with the pharmacopœial requirements. The first two were labeled, "Made to conform to the U. S. P. requirements." The last was distilled by the writer, and the others were secured from prominent distillers in this country and guaranteed pure. The Pharmacopœia requires the specific gravity to fall between 1.045 and 1.055, but "Die Aetherische Oele," by Gildemeister and Hoffmann, recognizes a specific gravity as low as 1.024. While the specific gravity is, to a certain extent, an indication as to

the amount of eugenol present, it would not be wise, in view of the above facts, to pronounce an oil adulterated simply because it had a specific gravity below 1.045.

Potassium cyanid 98 to 100 per cent pure has assumed considerable commercial importance. In ordering this article it is customary to specify the per cent of cyanid only. For financial and technical reasons potassium cyanid is largely mixed with sodium cyanid. There can be no real objection to this practice, if the goods are properly represented, but a mixture of these two cyanids should not be delivered for 98 to 100 per cent potassium cyanid. In determining the percentage of potassium cyanid in a mixture of this character the results will be above 100 per cent in proportion to the amount of sodium cyanid present. In order to meet this difficulty manufacturers add, or do not remove, certain inert substances, which usually consist of carbonates, chlorids, or mixtures of both.

An examination of four samples of potassium cyanid, labeled 98 to 100 per cent pure, gave the following results:

Analyses of 98 to 100 per cent potassium cyanid.

Sample No.	Cyanid (calculated as KCy).	Potassium cyanid.	Sodium cyanid.	Potassium carbonate, etc. (by difference).	Moisture at 125° C.	Sodium chlorid.
	Per cent.	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*
1	101	33.65	50.56	0.70	0.82	14.27
2	111.19	13.62	73.65	12.82	.....	.....
3	105.87	31.75	55.93	12.32	.....	.....
4	95.33	65.90	22.20	8.82	1.58	1.66

All of the above samples represent imported goods. The results are self-explanatory. No valid reason for the practice of mixing the cyanids in the manner shown and selling the mixture as potassium cyanid has thus far been offered by manufacturers.

METHODS OF ESTIMATING CHLORIDS IN SOLUBLE CYANIDS.

The present methods for detecting and estimating chlorids in the soluble cyanids are not satisfactory. It is usually stated that silver cyanid is soluble in concentrated nitric acid, whereas silver chlorid is insoluble, but in practice it is not safe to rely on this test. The fusion method is useful but dangerous. It consists in heating to redness an intimate mixture of 1 gram each of the cyanid and potassium nitrate and 5 grams of potassium carbonate. The carbonate and nitrate must be free from chlorids. In this mixture an extremely efficient oxidizing agent and one of the best-known reducing agents are brought together. When the mixture is fused, there is a more or less vigorous chemical reaction, and frequently an explosion results. A more expeditious and satisfactory method would therefore be welcome.

The gravimetric method on the next page is based on the fact that cyanids reduce permanganates.

In a 250 cc beaker, containing 150 cc of water, dissolve approximately 1 gram (accurately weighed) of the cyanid. Heat to boiling, then cautiously add about 2 grams of potassium permanganate or such a quantity that the solution after having been heated for one-half hour on the steam bath is still distinctly pink. Destroy the excess of potassium permanganate with oxalic acid, heat the mixture a few minutes on the water bath, and the precipitate will subside, leaving a colorless layer of liquid. Filter the solution hot, wash the precipitate on the filter paper with 200 cc of hot water, mix the filtrates, render distinctly acid with nitric acid, and heat the mixture to boiling. In this solution the chlorids are estimated in the customary manner.

Mr. J. K. Haywood, chief of the insecticide and agricultural water laboratory of the Bureau of Chemistry, employs a volumetric method with satisfactory results. It has been carefully compared with the above gravimetric process and found to accord with it uniformly. The method is as follows:

Weigh accurately in a weighing bottle about 10 grams of the substance, dissolve in water, and make up accurately to 1 liter. In an aliquot part of this solution estimate the cyanogen by titrating with a decinormal silver nitrate solution. The end reaction is shown by the appearance of a white cloudiness in the solution. Now add potassium chromate, as indicator, and titrate with the standard solution of silver nitrate until the appearance of the usual reddish-brown color of silver chromate.

The reactions involved in the above method are represented by the following equations:

(1) $AgNO_3+2KCN=AgCNKCN+KNO_3$.
(2) $AgCNKCN+AgNO_3=2AgCN+KNO_3$.
(3) $NaCl+AgNO_3=AgCl+NaNO_3$.

Representing the number of cubic centimeters of silver nitrate solution used in the first titration by A and the number of cubic centimeters used in the second titration by B, then B—A equals the number of cubic centimeters of decinormal silver nitrate solution required to combine with the chlorids present, while the amount of cyanogen can be calculated from A, as indicated by the first equation given.

INTENTIONAL ADULTERATIONS.

With very few exceptions the underlying motive of all intentional adulterations is monetary gain. Some of the sophistications considered above appear to have some superficial excuse for existing, but those here enumerated as intentional are deliberately premeditated misrepresentations, and should be dealt with summarily. In this category comes the potassium cyanid reported above. Other instances are: Borax diluted with sodium bicarbonate; cornstarch delivered when St. Vincent arrowroot is asked for; prime quality drugs mixed with

inferior or partially exhausted goods; spurious sandalwood oil containing chloroform added to raise the specific gravity and to increase the apparent content of santalol; powdered drugs in the preparation of which inert and deteriorated products have been used; beeswax with its numerous adulterations; turpentine diluted with kerosene, etc.

A sample of beeswax recently examined was found to contain 33 per cent of cassava starch. This variety of starch indicated that the adulteration was of southern origin. On inquiry it was found that about $800 worth of this fraudulent material had passed through the New York custom-house, having been imported from Mexico.

Another sample of beeswax on examination gave the following results: Melting point, 61.5° C.; specific gravity at 15° C., 0.959; acid number, 14.2; ether number, 73.6. These numbers do not materially differ from those usually recognized as normal for pure beeswax, except the acid number, which is a little low. A qualitative examination showed that this article consisted, for the greater part, of a high melting point ceresin and Japan wax, the mixture being probably flavored artificially to resemble the genuine product. New York is the home of the apiary which produced this remarkable beeswax.

The adulteration of beeswax with starch is discouraging, because it shows that the days of gross sophistication are not past; but to find a scientifically prepared mixture closely resembling beeswax is most deplorable, because it indicates that men of education are using their talents to serve a dishonest purpose.

The drug laboratory has in its possession a small amount of a flavoring agent, which has been exploited as of much service in beeswax adulteration, but the nature of its composition has not as yet been determined.

Twenty-five per cent of all turpentine, as usually purchased in small packages, is liberally adulterated with kerosene. The present analytical methods do not appear to be sufficiently refined to detect this adulterant with certainty when present in small quantities. Investigations are under way at present which it is hoped will remedy this defect.

SIFTINGS AND SWEEPINGS.

In the handling of drugs more or less of the finer particles escape from the bales, and in the larger warehouses the practice has been established of collecting this material from the floors, as occasion requires, and offering it to the trade at a low figure. The conditions under which these sweepings and siftings are accumulated and collected naturally lead to the belief that they are likely to be contaminated to a considerable degree. Products of the above character commonly met with are the cinchona barks, cochineal dust, pepper, tea, and senna leaves.

Some of the sweepings and siftings are utilized in extracting certain active principles, like caffeine from tea sweepings, and certainly nothing could be said against an economy of this kind, but the practice of using articles of this character in the manufacture of medicinal preparations should certainly be discountenanced. Some manufacturers frankly admit that this practice obtains in their works, but maintain that these goods are "just as good" as those for which a high price is paid.

Three bales of calisaya bark siftings, all containing foreign material, on examination gave the following results: The per cent of total alkaloids was 0.47, 3.6, and 4.7. The per cent of ether-soluble alkaloids was not determined in the first bale recorded, and was 1.9 and 2.7, respectively, in the last two. A good calisaya bark should not contain less than 6 per cent of total alkaloids nor less than 3.5 per cent of ether-soluble alkaloids.

Every bale of senna siftings and every bag of tea sweepings examined contained a goodly proportion of extraneous matter. Broken senna leaves are usually of good quality.

A COMMON METHOD OF DECEPTION.

A very significant editorial appeared in the British Food Journal,[a] from which the following extract is taken:

> The substitution of an imitation of some kind for the article actually asked for or desired by the purchaser is a particularly mean form of deception which is practiced nowadays to an almost incredible extent. It is astonishing and mournful that so many persons should be concerned in the initiation, fostering, and carrying on of so shameful a system, and that others are found who in speech and print seem willing to lend to it either their countenance or condonation.

Still more reprehensible is the practice of submitting a sample of prime quality and then, on receipt of an order, delivering goods of an inferior grade.

Some may think that the above method of deception does not obtain to any extent, but only a superficial investigation will show that it permeates many lines of business, and those who are responsible for the quality of the medicinal remedies supplied the unfortunate sick should ever exercise eternal vigilance. The following examples, which are typical of this practice, should serve to banish the remotest doubt. A sample of belladonna leaves contained by acid titration 0.438 per cent of total alkaloids. On receipt of the consignment delivered as per sample submitted, nine bales were tested with the following results: 0.12, 0.14, 0.11, 0.10, 0.13, 0.12, 0.13, 0.30, 0.11 per cent of total alkaloids. A sample of potassium bromid complied with U. S. P., 1890, requirements. The goods supplied were inferior in

[a] 1903, vol. 5, p. 97.

every respect. A podophyllin sample was of U. S. P. quality, but the article delivered contained much material insoluble in alcohol. A linseed-meal sample contained 33 per cent of pure oil. After placing an order on the strength of the sample, two carloads were delivered, which, on examination, proved to contain on the average 35 per cent of oil, having the following properties: Specific gravity at 15° C., 0.9055; acid number, 6; saponification number, 99.7. The oil extracted from the linseed meal was highly adulterated with mineral oil, which was added to the flaxseed meal after a part of the natural oil had been expressed. A sample of oil of wormwood of good quality was submitted, but the goods delivered were adulterated with turpentine. A sample of tea sweepings submitted contained 2.64 per cent of caffeine alkaloid. A ton subsequently delivered contained only 1.6 per cent of this alkaloid. A sample of caramel possessed a coloring equivalent of 100, and gave good tests in every respect. On examining a delivery of about 5,000 pounds it was found to have a coloring equivalent of only 80, and deported itself badly in every way. These examples could be largely extended, but the above fully illustrate existing conditions.

It will be observed that most of the examples cited represent the larger transactions and usually involve manufacturers and producers. Many members of the American Pharmaceutical Association and the National Wholesale Druggists' Association, and some of the best informed manufacturers and jobbers, have placed themselves on record as conversant with these undesirable methods and anxious to prevent their use, but they are greatly handicapped by competition. Such men hope to see the day when all druggists, retail or wholesale, will be compelled by some competent authority to deal only in high-class medicinal agents.

II.—ROSE GERANIUM OIL AND ITS SUBSTITUTES.

In spite of the great advance made in the chemistry of essential oils during the past decade, ample evidence can readily be collected to show that this is as yet a fertile field for the adulterator. Many kinds of manipulators are found, from the tyro who endeavors to palm off oil of French turpentine for oil of rue, and the distiller who sprinkles his rose leaves with geranium oil before distilling, to the chemist who is an abettor to the use of acetin and glycerin in volatile oils for the purpose of increasing the apparent content of ester and alcohol, respectively.

By referring to the various price lists it will be found that the quotations for the geranium oils vary from $12 per pound for the Spanish to $2.25 for the Turkish oil; and ginger-grass oil, which is conceded to be only another name for an inferior Turkish oil, sometimes highly adulterated, is quoted at $1.10 per pound. Certainly here seems to be a great opportunity for the clever manipulator, and aside from the assistance of a well-trained nasal organ, let us see what are the probabilities of detecting such adulteration.

Rose geranium oil is a colorless, yellowish, greenish, or brownish liquid, depending on the manner of distillation and storage, and has a pleasant rose-like odor. Its specific gravity varies from 0.8878 to 0.9073; optical rotation in a 100 mm tube, -6° to -16°; ester, calculated as geranyl tiglinate, varies from 8 to 42 per cent. All varieties are soluble in 2 to 3 volumes of 70 per cent alcohol, except the Spanish, which is rendered turbid by the presence of a small amount of separated paraffin. The chief constituents are geraniol and citronellol, the total content of which, both free and combined, varies from 60 to 85 per cent. The former usually exists in much the greater proportion.

Turkish or Indian geranium oil, also known as palma rosa, Indian grass oil, and rusa oil, usually closely resembles rose geranium oil in physical appearance, solubility, specific gravity, and percentage content of alcohols and esters. In odor there is frequently a close resemblance and the optical rotation varies from $+2^{\circ}$ to -2°.

Ginger-grass oil is supposed to be an inferior quality of palma rosa, and its properties, therefore, should very closely resemble those of the latter oil, excepting possibly its odor, unless it is highly diluted with turpentine or mineral oil, as is frequently the case.

It can readily be seen that a judicious mixer could combine oils possessing the properties described above so as to bewilder a chemist, even though he were well versed in the chemistry of essential oils.

Jeancard and Satie[a] have studied these oils to some extent, and think they can distinguish between them by their contents. The following table is taken from their work:

Analytical data on pure geranium oils.

Origin.	Density at 15° C.	Rotation at 15° C. in 100 mm.	Saponification value.	Esters.	Alcohols.
		°		*Per cent.*	*Per cent.*
Cannes	0.8972	−9.40	54.60	9.80	66.31
Spain	.9073	−7.30	65.80	7.84	66.23
Corsica	.9012	−8.00	60.20	7.00	68.55
Africa	.9006	−8.06	65.80	8.08	63.19
Bourbon	.8905	−8.20	74.00	6.65	71.28
India	.8960	− .48	43.00	11.30	84.62

The per cent of esters and alcohols is based on the formulæ $C_{12}H_{20}O_2$ and $C_{10}H_{18}O$, respectively.

In view of the fact that the highest-grade oils grow in certain localities only and bring fancy prices, the opinion is ventured that it would not be safe to deduce any general statement from the above results, except in the case of Indian oil.

Some time ago the writer received a number of samples of geranium oils in original packages bearing the labels of the largest and best-known essential-oil dealers in the world, with the request that an opinion be given as to their purity and quality. On submitting the samples to an examination the results tabulated below were obtained:

Analyses of geranium and allied oils.

Kind of oil.	Color.	Specific gravity at 15° C.	Acid number.	Esters as tiglinate.	Alcohols.	Opt. rot. in 100 mm tube at 20° C.	Solubility in 70 per cent alcohol.
				Per ct.	*Per ct.*	*Degrees.*	
African (1)	Greenish yellow	0.8901	4.51	20.48	76.06	− 6.73	Soluble in 2 volumes.
African (2)	Lemon yellow	.8915	6.00	28.95	63.49	− 8.41	Insoluble in 10 volumes.
African (3)	Orange yellow	.9053	6.09	18.95	42.34	−19.20	Do.
African (4)	Lemon yellow	.9319	4.47	95.00 (a 78.85)	71.08	− 7.70	Soluble in 1¾ volumes.
Algerian (1)	do	.8981	3.20	33.61	65.57	−17.00	Insoluble in 10 volumes.
Algerian (2)	Colorless	.8964	2.87	36.46	73.14	− 9.60	Soluble in 2½ volumes.
Reunion	Lemon yellow	.8878	6.28	28.89	72.13	− 7.66	Soluble in 2 volumes.
Palma rosa	Orange yellow	.8968	1.80	22.30 (a 18.50)	81.75	− 2.90	Do.
Turkish (1)	Lemon yellow	.9142	4.13	12.13 (a 10.06)	50.00	−50.70	Insoluble in 10 volumes.
Turkish (2)	do	.9154	2.41	14.25 (a 11.72)	72.93	+ 1.91	Soluble in 2 volumes.
Ginger grass (1)	do	.9213	1.50	8.07 (a 6.69)	20.18	−69.13	Insoluble in 10 volumes.
Ginger grass (2)	do	.9234	3.88	1.46 (a 1.20)	21.77	−65.00	Do.
Rhodonol II	Colorless	.8758	.....	9.00 (a 7.42)	.....	−26.9	Soluble in 2 volumes; insoluble in more.

[a] Per cent of ester calculated as geranyl acetate.

The acid number was determined by dissolving a given weight of the oil in strong alcohol, in which all the oils were soluble in all proportions, and titrating with decinormal alcoholic potash, at the ordinary temperature, using phenolphthalein as indicator. The figures

[a] Bul. Soc. Chim., 1900 (3), **23**: 37.

indicate the number of milligrams of potassium hydroxid required to neutralize the acidity of one gram of oil. The esters were estimated by adding an excess of alcoholic potash to the above solution, heating to boiling with a reflux condenser for about one hour, then titrating back the excess of alkali by means of decinormal acid. From the amount of alkali consumed the necessary calculations can readily be made, either as geranyl tiglinate ($C_{10}H_{17}CO_2C_4H_7$) or geranyl acetate ($C_{10}H_{17}CO_2CH_3$), as the case may require. The percentage of alcohol, free or combined, was determined by acetylizing a given weight of oil with an equal amount of acetic anhydrid, in the presence of fused sodium acetate. The acetylized product was purified by washing with water, and rendered anhydrous by means of fused sodium sulphate. A given weight of the acetylized oil was then saponified, as outlined above for determining esters, and from the data thus secured the desired calculations were made.

In computing the amount of alcohol, both free and combined, in geranium oil, it must be remembered that the chief ester of the natural oil is a tiglinate, and on acetylizing with acetic anhydrid the free alcohols are converted into acetic esters. We therefore have a mixture of esters on which to base our calculations. The percentages of alcohols given in the table above were computed from the mixed esters. The question might arise as to whether any of the tiglinic group was replaced by the acetyl group, but this inquiry can not be answered here.

The first African oil, the second Algerian oil, and the Reunion oil are normal in every respect. The African oil No. 2 and the Algerian oil No. 1 can be considered normal except as to solubility, and it is doubtful whether these oils can justly be considered adulterated. The third African oil is low in alcohol content, high in optical rotation, and insoluble in the proper amount of 70 per cent alcohol. The fourth African oil is a spurious product, which did not respond affirmatively for a hydroxyl group when tested by means of acetyl chlorid in the conventional manner, thus indicating the absence of any alcohol. The palma rosa oil and the Turkish oil No. 2 are both normal India products, while the first Turkish oil is abnormal. Both of the ginger-grass oils are entirely different from anything described in literature. Judging from the high specific gravities and high optical rotations, these ginger-grass oils are not adulterated with either turpentine or mineral oil. The last oil named, Rhodonol II, is apparently a fairly pure geraniol.

It is clearly evident from the data obtained in this investigation and other work on record that a scientific adulterator could readily mix some of the cheaper geranium oils with the expensive, high-grade products without much fear of detection by the analytical methods at present available. Apparently the only satisfactory procedure at our disposal for securing the proper quality of geranium oil is the use of well-trained olfactories.

III.—PHENACETIN: METHODS OF ANALYSIS AND COMMERCIAL STATUS.

HISTORICAL REVIEW.

On reviewing the history of phenacetin it soon becomes apparent that, like many other useful discoveries, it was not the achievement of a single individual nor of a certain time, but was gradually evolved by the successive efforts of many minds, stimulated by the progress of correlated branches of science. It was, however, due to the patient efforts of O. Hinsberg and his associates that the production of this article on a commercial scale was made possible and its great medicinal value became known to the world.

The germ of phenacetin was sown by the celebrated French chemist, A. Cahours, during the course of a series of valuable investigations extending over a number of years. In 1843[a] appeared his "Recherches sur l'huile de Gaultheria procumbens," which work was persistently continued until 1849,[b] when he announced the discovery of phenetol ($C_6H_5OC_2H_5$, phenol ethyl ether), mononitrophenetol ($C_6H_4NO_2OC_2H_5$), and phenetidin ($C_{14}H_9NO_2C_2H_2$, old nomenclature). Two methods for preparing phenetol were given; one by heating together ethyl salicylate and baryta, and the other by simply heating barium ethyl salicylate.

Following up a suggestion of Cahours, G. Baly,[c] at the request of A. W. Hofmann, prepared phenetol by the first method described above, but called it "salithol." Baly presented his work to the London Chemical Society December 4, 1848, but it did not appear in the society's official organ until 1850. It is interesting to note in this connection that several foreign journals printed the article in 1849, giving the Quarterly Journal of the Chemical Society credit for an article that did not appear in its columns until nearly a year afterwards.

In 1851 Cahours[d] prepared phenetol by heating potassium phenolate and ethyl iodid together in a sealed tube at from 100° to 120° C. The following year appeared C. Gerhardt's[e] classic "Recherches sur les acides organique anhydres." In this investigation we find prepared

[a] Comp. rend., 1843, **16**: 853; J. prakt. Chem., **29**: 197.

[b] Ann. Chim. Phys., 1849 (3), **27**: 439; J. prakt. Chem., 1850, **49**: 262; Ann. (Liebig), **74**: 314.

[c] Quart. J. Chem. Soc., 1850, **2**: 28; J. prakt. Chem., 1849, **47**: 419.

[d] Comp. rend., 1851, **32**: 60; Ann. (Liebig), **78**: 225.

[e] Comp. rend., 1852, **34**: 755; J. prakt. Chem., **56**: 321.

for the first time acetanilid and benzanilid, by the action of acetic anhydrid and benzoic anhydrid, respectively, on anilin. This same worker[a] had made benzanilid seven years before by the interaction of benzoyl chlorid and anilin.

In 1854 J. Fritzsche began to study the action of nitric acid on phenol. His first results were presented to the St. Petersburg Academy of Sciences November 6, 1857.[b] In this communication he reported the preparation of ortho-nitrophenetol by the action of ethyl-iodid on a silver salt of ortho-nitrophenol. The ester was extracted and purified by treating the mixture with ether, evaporating the solvent, and distilling the resulting reddish-yellow fluid. The product thus obtained was nearly odorless, almost insoluble in water, but readily soluble in alcohol and ether. Boiling caustic potash solution decomposed it with difficulty.

The following year[c] the same worker discovered and described isonitrophenic acid (para-nitrophenol) and some of its derivatives. The derivative of particular interest in this connection is its ethyl ester, para-nitrophenetol, prepared as was the ortho-nitrophenetol above. Para-nitrophenetol he described as a colorless crystalline body possessing an agreeable aromatic odor, nearly insoluble in water, soluble in ether and alcohol, and melting at 57° to 58° C.

Nothing of importance appeared again until A. Groll[d] announced the preparation of ortho-amidophenetol from ortho-nitrophenetol. The latter was prepared by dissolving potassium nitrophenolate and ethyl bromid in from 3 to 4 parts of alcohol and heating the mixture for a number of hours in a sealed tube at from 140° to 160° C. Ortho-amidophenetol was made by treating ortho-nitrophenetol with metallic tin and hydrochloric acid. From this time forward the nitrophenetols were well known to organic chemists, being frequently employed by them in their research work, and probably in the industrial world. Para-nitrophenetol was used by R. Schmitt and R. Möhlau[e] in their investigation on azoxy-azo- and hydrazo-phenetol, by Schmitt[f] during his study of the constitution of the dichlorazophenols, and R. Möhlau in his dissertation[g] very fully describes ortho-nitrophenetol. The latter, in his study of ortho-diamidodiphenetol,[h] fully sets forth that the phenetols were common property.

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[a] Comp. rend., 1845, **20**: 1031.

[b] St. Petersb. Bull. Classe phys. math., 1858, **16**: 161; J. prakt. Chem., **73**: 293; Chem. Centralb. (2), **3**: 171.

[c] St. Petersb. Bull. Classe phys. math., 1859, **17**: 145; J. prakt. Chem., **75**: 257; Ann. (Liebig), **110**: 155; Jahresb. (Liebig and Kopp), **11**: 407.

[d] J. prakt. Chem., 1875 (2), **12**: 207.

[e] J. prakt. Chem., 1878 (2), **18**: 198.

[f] J. prakt. Chem., 1879 (2), **19**: 312.

[g] Dissertation, Freiburg, 1879, i, B. 27, ff, through J. prakt. Chem., 1880 (2), **21**: 318.

[h] J. prakt. Chem., 1879 (2), **19**: 381.

By allowing fuming nitric acid to act on phenetol, Cahours[a] obtained a solid and a liquid body; the former he called dinitrophenetol and the latter mononitrophenetol. E. J. Hallock[b] repeated these experiments and obtained two similar bodies. He says:

> The solid, when purified by repeated recrystallizations, both from acid and from alcohol, was proved by an ultimate analysis to be a mononitrophenetol. Its melting point, 58° C., and other physical properties coincide with that of para-mononitrophenetol, prepared by Fritzsche in 1858 by the action of iodid of ethyl upon the silver salt of para-nitrophenol.

H. Andreae[c] in his excellent communication of nitro-ortho- and nitro-para-azophenetol shows that he was well acquainted with both the para- and the ortho-nitrophenetol. C. Willgerodt[d] gave a new method for preparing para-nitrophenetol, as indicated by the following equation: $C_6H_4(NO_2)Cl+C_2H_5OH=C_6H_4(NO_2)OC_2H_5+HCl$. H. Kolbe[e] gave additional methods for preparing these products. Other useful papers published bearing on these products were contributed by J. Berlinerblau,[f] C. Liebermann and St. Kostanecki,[g] and C. Willgerodt and M. Ferko.[h]

The next step involved in the production of the phenacetins is the conversion of the nitrophenetols into the amidophenetols. This is usually done by the well-known nascent hydrogen process.

Ortho-amidophenetol was first given to the world by A. Groll[i] in 1875. The same compound was produced by M. Förster[j] in 1880 and by J. Berlinerblau[f] in 1884. Meta-amidophenetol was well known to Berlinerblau,[f] and Ph. Wagner,[k] and undoubtedly to other organic chemists in the early eighties. The discovery of para-amidophenetol is generally credited to the American chemist, E. J. Hallock,[b] but R. Schmitt's[l] work on the constitution of the dichlorazophenols shows that chemists were well acquainted with this compound before the publication of Hallock's article. It was well known to Liebermann and Kostanecki[g] in 1884.

The process described in the phenacetin patent for the manufacture of para-phenetidin was old and well known prior to the date when the patent was granted—1889. Substantially the same method was described in 1884 by H. Köhler.[m]

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[a] Ann. Chim. Phys., 1849 (3), **27**: 465.
[b] Am. Chem. J., 1879, **1**: 271.
[c] J. prakt. Chem., 1880 (2), **21**: 318.
[d] Ber. d. chem. Ges., 1881, **14**: 2636; ibid., 1882, **15**: 1002.
[e] J. prakt. Chem., 1883 (2), **27**: 424; ibid. (2), **28**: 62.
[f] J. prakt. Chem., 1884 (2), **30**: 97.
[g] Ber. d. chem. Ges., 1884, **17**: 876.
[h] J. prakt. Chem., 1886 (2), **33**: 152.
[i] J. prakt. Chem., 1875 (2), **12**: 207.
[j] J. prakt. Chem., 1880 (2), **21**: 341.
[k] J. prakt. Chem., 1885 (2), **32**: 70.
[l] J. prakt. Chem., 1879 (2), **19**: 312.
[m] J. prakt. Chem., 1884 (2), **29**: 257.

Meta-acetphenetidin, or the meta variety of phenacetin, was prepared by Ph. Wagner[a] in 1885. This he accomplished by gently heating together two parts of meta-phenetidin and one part of acetic anhydrid, cooling the resulting mixture, transferring the cooled crystalline mass to a funnel, washing out part of the impurities by means of water, and finally recrystallizing from hot water. The purified, glistening crystals were white, with a tint of red, melted at 96.7° C. (uncorrected), and were difficultly soluble in water.

After having prepared para-amidophenetol, Hallock[b] experimented further with this compound and reported one observation in the following words: "This oil combines, like anilin, directly with acetyl chlorid to a crystalline solid." This crystalline solid, for the greater part, undoubtedly consisted of para-acetphenetidin, or phenacetin proper. Hallock, however, did not isolate the crystalline body and establish its physical properties and chemical composition. If he had done this it would have been a positive anticipation of the patent, and that part of the patent alleging novelty or "a new pharmaceutical product" would have had its mainstay undermined. All information about the crystalline body was left vague and inconclusive by Hallock, who evidently did not think that it possessed any value or was worth further investigation. The statement that he obtained such a body by the interaction of acetyl chlorid and para-amidophenetol was not useful to the public.

The great desideratum with the medical profession has been a safe, effective, and inexpensive antipyretic. The oldest and best febrifuge at this time (1880) was quinine sulphate, but on account of its costliness many efforts had been made by chemists either to prepare quinine artificially or to find an efficient substitute. In 1842 Gerhardt[c] distilled a mixture of quinine, water, and caustic potash and obtained a useful base which he called chinolin. Its high price from this source forbade its use medicinally, but by treating the alkaloid cinchonin in a similar manner he produced the same base. He was very much encouraged by the results of this investigation, for it was found that this comparatively cheap base and its salts were active antipyretics. Chinolin tartrate was the earliest largely used artificial febrifuge. Chinolin itself was used as a nucleus of many synthetic antipyretics or quinine substitutes. The successful preparation of synthetic quinine has been reported from time to time, but at this writing has not been accomplished. Stimulated by the success of Gerhardt, K. Hlasiwetz and L. Barth[d] distilled resins in the same manner in which quinine

[a] J. prakt. Chem., 1885 (2), **32**: 70.
[b] Am. Chem. J., 1879, **1**: 271.
[c] Ann. (Liebig), 1842, **42**: 310; J. prakt. Chem., **28**: 65.
[d] Wien. Akad. Ber., 1864, **49**: 203; through Chem. Centralb., (2), **9**: 806.

and cinchonin had been distilled and obtained a product which they called resorcin. This chemical was at first extolled as an antipyretic also.

From 1862 to 1879 there appeared to be a cessation of activities in the field of this class of remedies, but at the latter date W. Königs[a] gave a new impetus to the work by his researches on chinolin, making it synthetically on a large scale from anilin. He was soon joined in his investigations by Baeyer, Skraup, Fischer, Knorr, Körner, and others, with very fruitful results.

Doctors Fischer and Königs in their studies on the alkaloids came to the conclusion that the properties of quinine did not reside in the quinolin nucleus, but in an oxygen or hydrogen-bearing element contained in or introduced into the nucleus. With this in mind their researches were prosecuted, and a number of new bodies were discovered, only two of which, however, appeared to be successful as medicinal agents. These were oxyhydromethylchinolin hydrochlorid, prepared by O. Fischer[b] and called "Kairin," and tetrahydromethylquinolin or tetrahydroethylquinolin, made by L. Hoffmann and W. Königs[c] and named "Kairolin." The former was patented, highly extolled, and extensively advertised, and seems to have been the first medicinal chemical that was stimulated by the mercantile influence of letters patent.

In 1884, L. Knorr[d] succeeded in preparing another very efficient antipyretic and named it antipyrin. It was well covered by patents. In France, however, a patent was granted only on a process for manufacturing it as an anilin product. But antipyrin did not possess any industrial value and could not be sold as a patented remedy, for France, in the endeavor to hold the interests of suffering humanity above the interest of the individual inventor, does not grant patents on medicinal agents. The result was that antipyrin was not employed openly in France during the life of the patent.

Acetanilid was discovered in 1852 by C. Gerhardt,[e] but its antipyretic properties were not revealed until 1886, by G. Krieger.[f] It is well known by its trade name Antifebrin. This compound unfortunately is prone to induce collapse when frequently administered in large doses. It was shown twenty years previous to this time by C. D. Schroff,[g] A. Crum-Brown, and T. R. Fraser,[h] and more recently

[a] Ber. d. chem. Ges., 1879, **12**: 453.

[b] Ber. d. chem. Ges., 1883, **16**: 712; Arch. d. Pharm. (3), **21**: 617.

[c] Ber. d. chem. Ges., 1883, **16**: 727.

[d] Ber. d. chem. Ges., 1884, **17**: 2032; J. Soc. Chem. Ind., 1885, **4**: 59.

[e] Comp. rend., 1852, **34**: 755.

[f] Centralb. f. Klin. Med., 1886, **7**: 761.

[g] Wochenblatt d. K. K. Ges. Aerzte, Wien, 1866, **6**: 157.

[h] Trans. Royal Soc. Edin., 1867 to 1869, **25**: 151 and 693; J. Anatomy and Physiol., (2), **3**: 478.

by Stolnikow,[a] that a modification of the chemical constitution of a chemical compound materially changes its physiological action. For example, the introduction of a methoxy group into morphine, converting it into codeine, materially diminishes its narcotic action.

Salol was prepared by M. Nencki[b] and investigated therapeutically by Dr. Sahli.[c] This chemical was fully covered by patents.

In 1887 phenacetin, as an antipyretic, first made its public appearance through communications by G. Kobler[d] and E. Ghillany.[e] This chemical was prepared by Hinsberg. No unfavorable after symptoms were noticed in 50 cases that were treated. O. Hinsberg and A. Kast[f] reported that para-acetphenetidin (phenacetin) in doses of 3 grams acted like a strong poison, but in doses from 0.2 to 0.5 gram, exhibited to feverish persons, it was an effective antipyretic.

E. Utescher[g] reported phenacetin as a very reliable antipyretic and singularly free from secondary effects. He described it as an odorless, tasteless, white (pinkish tint), crystalline body, having a melting point of 132.5° C. When heated with sulphuric acid, ethyl acetate is produced. On heating a mixture of phenacetin, potassium hydroxid solution, and chloroform the isonitril odor is developed. Phenacetin heated with a potassium hydroxid solution liberates ethyl alcohol, which, on the addition of iodin, gives iodoform. This phenacetin was manufactured by F. Bayer & Co.

The above historical review quite fully sets forth the state of the art and knowledge prior to the application for the phenacetin patent, June 29, 1888. The various methods of making acetanilid and its physiological action were well known. Acetanilid produced unfavorable after results when given in repeated large doses. Some undesirable physiological actions had been removed or modified or mitigated by the introduction of certain well-known groups. Phenacetin has the same chemical constitution as acetanilid, excepting that one of the atoms of hydrogen of acetanilid has been substituted by an ethoxy group.

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[a] Ztschr. f. Physiol. Chem., 1884, **8**: 235.
[b] Polytech. Notizbl., 1886, **41**: 176; through Chem. Centralb., (3), **17**: 751.
[c] Therap. Monatsh. Berl., 1887, **1**: 333.
[d] Ztschr. Österr. Apoth. Ver., 1887, **25**: 323.
[e] Ztschr. Österr. Apoth. Ver., 1887, **25**: 339; J. Soc. Chem. Ind., **6**: 676.
[f] Centralb. Med. Wissensch., 1887, **25**: 145.
[g] Apoth. Ztg., 1887, **2**: 436; through J. Chem. Soc. Ind., **7**: 227.

PHENACETIN PATENTS AND TRADE-MARKS.

UNITED STATES PATENT OFFICE.

Oskar Hinsberg, of Barmen, Assignor to the Farbenfabriken, Vormals Fr. Bayer & Co., of Elberfeld, Germany.

PHENACETINE.

Specification forming part of letters patent No. 400086, dated March 26, 1889. Application filed June 29, 1888. Serial No. 278593. (Specimens)

To all whom it may concern:

Be it known that I, Oskar Hinsberg, a citizen of the Empire of Germany, residing at Barmen, in the said Empire, have invented a Useful Improvement in the Manufacture of a New Pharmaceutical Product, of which the following is a specification.

My invention relates to the production of a new pharmaceutical product, a new antipyretic and antineuralgic, obtained by reducing nitrophenetole and melting the phenetidinchlorhydrate thus formed with dried sodium acetate and acetic acid.

In carrying out my process practically I proceed as follows: Fifty kilos of the potassium salt of paranitrophenole are mixed with three hundred kilos of alcohol, adding forty kilos of bromaethyl. The mixture is heated in an autoclave at a pressure of three to four atmospheres during about eight hours. At this time the reaction is finished, whereby paranitrophenetole is obtained according to the following equations:

$$C_6H_4(ONa)(NO) + C_2H_5Br = C_6H_4(OC_2H_5)(NO_2) + BrNa$$

In order to separate the mononitrophenole, which has not taken any part in the process, from the ether recently formed, the solution is treated with steam. By this operation the ether distills, leaving behind the paramononitrophenole.

For the reduction of the paranitrophenetole forty kilos of this ether are mixed with sixty kilos of muriatic acid and sixty kilos of water. To this mixture are gradually added, at a temperature of 70° centigrade, twenty-five kilos of iron filings, the whole being stirred continually. As soon as the ether is entirely reduced, paraamidophenetole is obtained, as explained by the following equation:

$$C_6H_4(OC_2H_5)(NO_2) + H_6 = C_6H_4(OC_2H_5)(NH_2) + 2H_2O$$

The solution obtained in this manner is saturated with chalk diluted with water, and for the purification of the amido compound treated with steam the distillate is absorbed in water acidulated by muriatic acid. The muriatic salt of the paraamidophenetole crystallizes in white leaves. Fifty kilos of this product are melted with one molecule of melted acetate of sodium and twenty four kilos of glacial acetic acid. The melted mass is repeatedly boiled with water and the new monoacetylparamidophenetole obtained from the filterates after cooling. It has the following chemical formula:

$$\text{Para } C_6H_4(NH(C_2H_3O))(OC_2H_5) = C_{10}O_2H_{13}N$$

and is obtained according to the following equations:

$$\text{Para } C_6H_4(NH_2)(OC_2H_5) + CH_3COOH = C_6H_4(NHC_2H_3O)(OC_2H_5) + H_2O$$

The monoacetylparamidophenetole crystallizes in white leaves, melting at 133° to 136° centigrade. It is tasteless, little soluble in cold water, more so in hot water, but easily in alcohol, chloroform, benzole, etc. It is altogether different from the body described in the *Year Book of Pharmacy*, 1883, page 146, denominated "phenacetëine". The formula of phenacetëine is $C_{10}H_{12}O$, that of phenacetine $C_{10}H_{13}O_2N$, my product containing nitrogen contrary to phenacetëine. The phenacetëine represents a coloring matter, an armorphous carmine red powder, the acid solution of which is yellow, the alkaline raspberry red, while my phenacetine is colorless, crystallizing in white leaves, not changing color by addition of acids or alkalies.

Having thus described my invention, what I claim as new, and desire to secure by Letters Patent, is—

The product herein described, which has the following characteristics: it crystallizes in white leaves, melting at 135° centigrade; not coloring on addition of acids or alkalies; is little soluble in cold water, more so in hot water; easily soluble in alcohol, ether, chloroform, or benzole; is without taste and has the general composition $C_{10}H_{13}O_2N$.

O. Hinsberg.

Witnesses:
Wm. Diestel,
O. J. Heimpel.

A patent on phenacetin was granted to O. Klimmek,[a] of Chicago, Ill., under the chemical name oxyethylacetanilid. This patent was subsequently found to be invalid.

On reading the phenacetin patent (Hinsberg) it will be observed that this patent is for the product and the descriptive portion or specification sets forth a process by which this product is made. In an attack on the validity of the patent the patentees took shelter behind this claim, alleging that the invention resided in the product and not in the process. The patentee undoubtedly felt that there was nothing new in the process described, and it was a necessity to draft the patent in such a manner as to permit the above construction. There is nothing new in the process. Every step was well known to chemists long prior to the time of application for the patent. The only useful improvement in the process was its application on a commercial scale, and there could have been little hope of successfully defending such a process in case of an attack. The claim for the product seems to be quite safe, for there is nothing available in ordinary chemical literature that conclusively anticipated the patent. The "crystalline solid" of Hallock, spoken of above, was undoubtedly impure phenacetin, but his information concerning the product was not sufficient anticipation, in the opinion of the courts, to invalidate a useful patent.

The patent has been declared good and valid in law by the United States circuit court[b] for the eastern district of Pennsylvania, and the United States circuit court of appeals[c] for the third circuit affirmed the decision of the lower court. O. Hinsberg must therefore at present be considered the acknowledged discoverer of phenacetin.

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[a] U. S. Pat. No. 606288, June 28, 1898.

[b] Dickerson et al. *v.* Mauer, Fed. Rept., 1901, **108**: 233.

[c] Mauer *v.* Dickerson et al., Fed. Rept., 1902, **113**: 870.

Phenacetin is an eminently efficient medicinal remedy, and is consequently largely used in all parts of the civilized world. It is open to competition in every country except the United States. This situation has caused the pharmaceutical profession of the United States to chafe considerably for many years. They think such a discrimination is an injustice. In many cases the burden became unbearable, and an illegitimate product began to be smuggled into this country from the Canadian borders. At present it is mostly brought in by unauthorized agents through the customs, duty paid, and delivered to the trade at about half the price charged by the holders of the patent. Much of this smuggled phenacetin bears the same label as the authorized product, but it is expressly stated on the carton that "The resale and importation to the United States of America is prohibited." It is sometimes called "peddled" phenacetin. In some cases the dealers in these goods are not satisfied with their profits, but mix the phenacetin with acetanilid and put it up in spurious packages closely resembling the original cartons. Adulterated phenacetin has caused the druggists of this country much trouble.

For a time it was thought that phenacetin could be handled in this country under its chemical name, para-acetphenetidin, as were dermatol (bismuth subgallate), antifebrin (acetanilid), and antipyrin (dimethyloxychinizin), and as aristol (dithymol di-iodid) is at present; but the court held that the phenacetin patent covered this name[a] also. Whatever may be the status quo, it is quite evident that very little para-acetphenetidin as such finds its way into the United States except such as is brought in surreptitiously.

The words "Phenacetin" and "Phenacetin-Bayer" are protected by United States registered trade-marks, numbers 18637 and 16392, respectively. If the usual custom should prevail, the owners of these trade-marks would have the exclusive right to use these words for thirty years from date of registration, but according to certain recent United States Supreme Court decisions[b] the word "Phenacetin" becomes public property at the expiration of the phenacetin patent; otherwise it would be necessary to use the chemical name or coin a suitable one for common use, as was the case with vaseline, known in the United States Pharmacopœia, 1890, as petrolatum. The following interesting extract is taken from the Singer decision:

Trade-mark—Doctrine as to Use of Name Given to Patented Article After Expiration of Patents.—It is the universal American, English, and French doctrine that where, during the life of a monopoly created by a patent, a name, whether it be arbitrary or be that of the inventor, has become by his consent, either express or

[a] Dickerson *v.* Tinling, Fed. Rept., 1897, **84**: 192.

[b] Official Gazette, 1896, **75**: 1703, Singer Manufacturing Company *v.* June Manufacturing Company; Official Gazette, 1901, **97**: 958, The Holzapfel's Composition Company (Limited) *v.* The Rahtjen's American Composition Company.

tacit, the identifying and generic name of the thing patented, this name passes to the public with the cessation of the monopoly which the patent created.

Same, same—Use of Name to Deceive.—Where another avails himself of this public dedication to make the machine and use the generic designation, he can do so in full forms, with the fullest liberty, by affixing such name to the machines, by referring to it in advertisements, and by any other means, subject, however, to the condition that the name must be so used as not to deprive others of their rights or to deceive the public, and, therefore, that the name must be accompanied with such identifications that the thing manufactured is the work of the one making it as will unmistakably inform the public of that fact.

On the principles embodied in the above decision the trade-marked names Antipyrin, Castoria, and Lanolin have become public property. Any one is at liberty to manufacture the above articles, with the restriction that the public must not be deceived as to the maker.

The underlying principle of our patent laws is to stimulate and protect invention. As a patent covering a new product prevents the production of the article during its life by other processes, even those which may be more economical, the inventor of a new process for the preparation of a patented product will be prevented by the owner of the product patent from practicing his new process during the life of the patent. To this extent the patent laws may be said to temporarily discourage the invention of new and more economical processes for the production of such patented products; but if to remedy such difficulty the protection by patent should be removed from this class of products these would be left unprotected as a class of useful inventions. It is generally admitted that our patent laws do work hardships in a few cases like phenacetin, but if they were modified so as to remedy such difficulties much greater ones would become involved. Though inequalities exist, our patent laws as a whole are considered by those who have made a study of the subject to be the best in the world.

The commission appointed by President McKinley to revise the United States patent and trade-mark laws did not see its way clear to make the changes desired by the American Pharmaceutical Association. For this the commission has been criticised harshly by the pharmaceutical press, which expresses surprise that the recommendations of the association named were ignored. While the recommendations appear to be reasonable, it must be remembered that our patent laws are general, and of the large number of patents granted in the United States chemicals and medicinal remedies constitute only a small percentage. Such changes would involve special (class) legislation for a comparatively few articles, which Congress is very much disinclined to enact, for experience has shown that the results are frequently far from satisfactory.

METHODS OF MANUFACTURE.

The method described in the patent does not need to be considered further. The following equations serve to illustrate the successive steps and the principles involved in the manufacture of phenacetin:

$$C_6H_4NO_2OH + 6H = C_6H_4NH_2OH + 2H_2O.$$
p-nitrophenol + nascent hydrogen = p-amidophenol + water.

$$C_6H_4NH_2OH + C_2H_5Br = C_6H_4NH_2OC_2H_5 + HBr.$$
p-amidophenol + ethyl bromide = { p-amidophenetol or p-phenetidin } + hydrobromic acid.

$$C_6H_4NH_2OC_2H_5 + CH_3COOH = C_6H_4NHC_2H_3OOC_2H_5 + H_2O.$$
p-phenetidin + glacial acetic acid = phenacetin + water.

Acetic anhydrid or acetyl chlorid can be used in place of glacial acetic acid. Phenacetin is obtained pure by recrystallization from hot water. In 1888 J. D. Riedel[a] took out a German patent for the manufacture of p-amidophenetol, which is the direct antecedent of phenacetin, by reducing 10 kg of diethyldioxyazobenzol with 6 kg of tin and 50 kg of 20 per cent hydrochloric acid. As soon as the diethyldioxyazobenzol is dissolved the mixture is rendered alkaline and submitted to distillation. Para-amidophenetol is carried over with the aqueous distillate. The patentee states that this chemical is serviceable in preparing phenacetin. The reaction is represented by the following equation:

$$C_2H_5OC_6H_4NNC_6H_4OC_2H_5 + 4H = 2C_2H_5OC_6H_4NH_2.$$

According to another method.[b] 50 grams of chrysophenin, 100 grams of zinc dust, and 250 cc of hot water are mixed in a 2-liter flask and heated on a water bath with frequent agitation for one hour, then submitted to distillation. The p-amidophenetol is removed from the distillate by means of ether and the ethereal solution rendered acid with 30 cc of dilute hydrochloric acid, which converts the phenetol into an ether insoluble hydrochlorid. The ether is drawn off and the aqueous solution concentrate to crystallization.

H. N. Morse[c] in 1878 treated p-amidophenol with acetic acid with the expectation of getting an acetic acid salt of p-amidophenol, but obtained p-acetylamidophenol. In 1894 E. Taüber[d] secured letters patent in Germany for a process that converts this chemical into phenacetin. The method is as follows: Mix 150 grams of p-acetamidophenol, 165 grams of potassium ethyl sulphate, 40 grams of sodium hydrate (dissolved in 500 cc of 60 per cent alcohol) in an autoclave

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[a] D. R. Patent No. 48543, Dec. 28, 1888.

[b] Bender und Erdmann, Organische Präparate, 1894, 2: 466.

[c] Ber. d. chem. Ges., 1878, **11**: 232.

[d] D. R. Patent No. 85988, June 19, 1894.

and heat the mixture for four hours at 150° C. On diluting the resulting solution with three parts of water the phenacetin separates out in fairly pure crystals. This appears to be the method now used in the manufacture of phenacetin.

The chemical constitution of phenacetin can readily be made out from what has been said above. Its chemical names are p-acetaminophenol ethyl ether, p-acetphenetidin, p-acetamidophenetol, ethoxyacetanilid, and oxyethylacetanilid. The last two names show their close relation to acetanilid. This is also shown by the following formulæ:

$$C_6H_5NHC_2H_3O \text{ (acetanilid) and } C_6H_4\begin{cases}NHC_2H_3O\\OC_2H_5\end{cases} \text{ (phenacetin).}$$

These two compounds resemble each other not only in chemical constitution, but also in their physical properties.

PHYSICAL AND CHEMICAL TESTS.

THE MELTING POINT.

Many and varied have been the tests proposed for establishing the purity of phenacetin, but at present the most reliable is its melting point, which is near 135° C. This important constant is disturbed by the presence of any impurity, such as unconverted p-phenetidin, acetanilid, antipyrin, salicylic acid, quinine sulphate, starch, milk sugar, etc. All powders so far examined in this laboratory having a melting point within 1 degree of normal have deported themselves in every respect like pure phenacetin.

The presence of unconverted p-phenetidin [a] in phenacetin is detected by melting 2.5 grams of pure crystal chloral hydrate in a test tube on a water bath, then adding 0.5 gram of phenacetin, and continuing the heating for a short time. If the phenacetin is pure, only a pinkish color develops on prolonged heating, whereas the presence of p-phenetidin (p-amido-phenetol) gives within five minutes an intensely red or reddish-violet coloration.

The one adulterant of phenacetin which appears to be difficult of detection is acetanilid. Its influence on the melting point of phenacetin was noted by E. Utescher,[b] who found that phenacetin mixed with 5 per cent of acetanilid shows, at from 113° to 114° C., minute drops of liquid on the sides of the capillary tube and melts completely at from 127° to 128° C. H. Schweitzer [c] studied the melting points of various mixtures of phenacetin and acetanilid and observed the strange phenomenon that all mixtures of these two chemicals began to melt at 92° C. Neither phenacetin nor acetanilid shows the least change at

[a] Pharm. Ztg., 1891, **36**: 185, through J. Soc. Chem. Ind., **10**: 799.
[b] Apoth. Ztg., 1888, **3**: 483, through Ztschr. anal. Chem., **27**: 666.
[c] J. Soc. Chem. Ind., 1895, **14**: 852.

this temperature. Schweitzer thinks this test is positive in identifying mixtures of these chemicals and that further examination is useless. The following table is taken from his communication:

Melting points of mixtures of phenacetin and acetanilid (Schweitzer).

No.	Mixture consisting of—		Begins to melt at—	Completely transparent at—
	Phenacetin.	Acetanilid.		
	Per cent.	*Per cent.*	°C.	°C.
1	99	1	92	134
2	95	5	92	133
3	85	15	92	128
4	66⅔	33⅓	92	126
5	60	40	92	125
6	50	50	92	122
7	40	60	92	118
8	33⅓	66⅔	92	114
9	15	85	92	110
10	5	95	92	106
11	100	0	133	134.5
12	0	100	112	114

Examinations made in this laboratory of mixtures of phenacetin and acetanilid gave the following results:

Melting points of mixtures of phenacetin and acetanilid (drug laboratory).

No.	Percentages in mixture of—		Melting point.	
	Phenacetin.	Acetanilid.	Begins to melt at—	Completely transparent at—
	Per cent.	*Per cent.*	°C.	°C.
1	90	10	96	127
2	75	25	92	121
3	50	50	90	92
4	25	75	90	99
5	10	90	95	110
6	100	0	133.5	134.8
7	0	100	112	113.8

The above observations were made several times on finely powdered anhydrous thoroughly mixed material with a standard thermometer, the entire mercurial column being in the heating medium. The melting points were taken in a long capillary tube attached to the thermometer, and both were placed in a test tube 20 cm long and 2 cm in diameter. The test tube was then filled with glycerin and placed in a liter Erlenmeyer flask nearly filled with glycerin. The temperature was gradually raised and kept uniform throughout the mass by a continual current of air. The results are not in perfect accord with Schweitzer's. The various mixtures began to soften at about 92° C., but not uniformly at that temperature.

Since these determinations were made an article by G. M. Beringer[a] has appeared, from which the following table on the melting points of mixtures of acetanilid and phenacetin is taken:

Melting points of mixtures of acetanilid and phenacetin (Beringer).

Acetanilid.	Shrinks.	Softens.	Melts.	Complete fusion.
Per cent.	°C.	°C.	°C.	°C.
1	126	128	131–132	134
2	115	125	130–131	132
3	110	124	128–129	131
4	105	120	125–126	130
5	100	108	112–114	124
10	100	105	110–112	120
15	95	105	110–112	120
20	92	100	105–106	118
25	90	94	95–96	115
30	90	92	94–95	115
35	85	90	92–94	108
40	84	90	91–93	105
45	82	90	92–93	100
50	80	86	90–92	96
55	77	86	90–92	95
60	82	88	90–92	94
65	82	87	90–92	94
70	87	90	91–92	95
75	88	90	92–93	96
80	88	90	91–92	99
85	90	92	95–96	105
90	92	95	100–101	108
95	96	102	107–108	111

These results do not add anything to what has already been noted, but they do show clearly, first, that chemists have not yet thoroughly learned how to determine the point at which a substance melts or begins to soften; and, second, that all mixtures of phenacetin and acetanilid do not begin to soften uniformly at 92° C.

SOLUBILITY.

The solubility of phenacetin is of service in detecting such adulterants as sodium bicarbonate, sugar, starch, quinine sulphate, and antipyrin.

CHEMICAL TESTS FOR ACETANILID IN PHENACETIN.

Numerous chemical tests have been proposed to detect the presence of acetanilid in phenacetin, but so far the ideal method has not been found. These two chemical bodies bear such a close resemblance to each other that it is difficult to detect the cheaper acetanilid in the more expensive phenacetin. The reverse is quite easy to accomplish. The following tests are given in the order of their usefulness.

Bromin Test (E. Hirschsohn).[b]

Boil 0.1 gram of the suspected mixture with 10 cc of water for several minutes, cool, filter, and to the filtrate add bromin water until a yellow coloration is produced. With phenacetin no turbidity results,

[a] Drug. Circular, 1903, **47**: 184.
[b] Pharm. Ztschr. f. Russ., 1888, **27**: 794.

but the presence of acetanilid causes a precipitate of p-bromacetanilid which melts at from 166° to 168° C. This test is recognized in the British and German pharmacopœias.

Saponification Test (P. N. Raikow and P. Schtarbanow).[a]

This test is based on the fact that acetanilid decomposes more readily with a fixed alkaline solution than phenacetin. It is applied as follows:

In a test tube of suitable size, provided with a perforated rubber stopple carrying a bent tube about 20 cm long, place 1 gram of acetanilid or phenacetin or a mixture of the two and 8 cc of a 25 per cent solution of potassium hydroxid and submit the mixture to distillation. Receive the distillate in a second test tube containing about 5 cc of a good bleaching-powder solution. With acetanilid alone a violet blue or purplish coloration develops, due to the anilin distilled; with phenacetin a brick-red opalescent solution forms by the interaction of the phenetidin and calcium hyperchlorite; with a mixture of phenacetin and acetanilid the first few drops of the distillate give the violet-blue coloration, while the latter portion of the distillate, received in a separate test tube, gives a brick-red turbidity and some coloration. With a considerable quantity of phenacetin the color becomes intensely red and the turbidity increases. In order to clearly differentiate between these two colorations it is necessary to collect the first few drops of the distillate for the acetanilid test and the latter portion for the phenacetin test. If this precaution is not carefully observed the phenetidin color reaction will obscure the anilin test, and the results are valueless. If acetanilid is not present the first few drops of the distillate will not produce any coloration with the calcium hyperchlorite solution.

G. M. Beringer[b] has studied this method very thoroughly and suggests several changes which he thinks materially improve it. By replacing the chlorinated-lime solution with a chlorinated-soda solution the end color reactions obtained become much more characteristic. With this reagent, acetanilid gives a decidedly purple tint not in the least obscured by a cloudy brownish-red, as is the case with the chlorinated-lime solution. With phenacetin the sodium-hyperchlorite solution changes to a "bright orange" (brick-red) and remains clear. The chlorinated-soda solution is considered to be a far more delicate and satisfactory reagent. Beringer says that he did not have any difficulty in detecting 3 per cent of acetanilid in phenacetin.

Another modification of this test suggested by the same writer is to heat together for one minute 0.1 gram of the substance and 3 cc of a sodium-hydroxid solution, cool thoroughly, add 5 cc of a chlorinated-soda solution, shake well, and set aside for a few minutes. If phenacetin only is present the upper layer is never of a deeper tint than

[a] Oesterr. Chem. Ztg., 1900, 3: 125. [b] Drug Circular, 1903, 47: 184.

yellow, but the presence of acetanilid imparts to it a purplish-red shade.

Other modifications are given, but the following is considered the most delicate: Intimately mix 1 gram of sodium peroxid with 0.1 gram of the substance to be tested, place the mixture in a 15 cm test tube, and add 3 cc of water. After the vigorous action ceases, shake thoroughly, cool, and add 5 cc of sodium-hyperchlorite solution, again shake vigorously, and set aside. If the phenacetin is pure the liquid remains colorless, or, at most, after long standing assumes a pale-yellow color, while the presence of acetanilid gives a purplish-red tint shading to pink, depending upon the amount of the adulterant present.

Judging from the chemical composition of phenacetin and acetanilid and the final color reactions, it is quite probable that the sodium peroxid acts mainly as a saponifying agent, as does potassium hydroxid in the original method.

Mercurous Nitrate Test (P. C. Plugge).[a]

Boil together 0.5 gram of phenacetin and 8 cc of water, cool and filter. To the filtrate add a fragment of potassium nitrite and 0.5 cc of dilute nitric acid and boil the mixture a few minutes. Then add 1 cc of mercurous nitrate solution containing nitrous acid, boil again, and if a red color develops acetanilid is indicated.

Iodophenol Test.[b]

This test was adopted by the German Pharmacopœial Commission for the identification of acetanilid, and is recognized by the fourth edition of the German Pharmacopœia, but the reaction has been proved to be worthless. Phenacetin responds affirmatively to this test, which is executed as follows:

Heat together for a few minutes 0.2 gram of acetanilid and 2 cc of 25 per cent hydrochloric acid. A clear solution results, which, with 4 cc of a 5 per cent solution of carbolic acid and a suitable amount of a good calcium hypochlorite solution (1 in 10) gives a dirty violet-blue color. On rendering this solution alkaline with ammonia water an indigo blue develops. The test has been modified in various ways, but so far the results are not satisfactory.

Isonitril Reaction.

This test was originally proposed by A. W. Hofmann[c] as characteristic of anilin. It has, however, been found that primary amines in general respond to this reaction. It is therefore a group reaction and can not with safety be employed to detect one compound containing

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[a] Arch. d. Pharm., 1890, **228**: 9; J. Anal. Appl. Chem., **7**: 77.

[b] Arch. d. Pharm., 1887, **225**: 1042.

[c] Ber. d. chem. Ges., 1870, **3**: 767.

an amido group in the presence of another compound containing the same group, even though one is more readily acted on by the agents employed than the other. The test is applied by heating together for a few minutes about 0.5 gram of the substance and 5 cc of a 10 per cent solution of sodium hydroxid, then cautiously adding a few drops of chloroform and setting the mixture aside for a few minutes. If a primary amine is present the characteristic offensive odor of phenylcarbamine can readily be detected. This reaction has received official sanction in the pharmacopœias of the United States, England, and Germany, and is so frequently cited as suitable for detecting acetanilid in phenacetin that a short résumé of some of the misleading statements made concerning it is desirable.

CONFLICTING STATEMENTS REGARDING THE ISONITRIL REACTION.

As early as 1887 Utescher[a] found that after heating phenacetin, sulphuric acid, and alcohol together, rendering the mixture distinctly alkaline with a fixed alkali, and adding a few drops of chloroform, the repugnant odor of carbylamine was developed. The sulphuric acid probably decomposes the phenacetin into acetic acid and phenetidin ($C_6H_4 NH_2 OC_2H_5$).[b] Schwartz[c] states that a simple method for determining acetanilid in phenacetin is by means of the isonitril reaction. W. Lenz,[d] in his review of special analytical methods, says that it is self-evident that for the detection of acetanilid in phenacetin the well-known "isonitril reaction" can be employed. Again, this author states that a mixture of acetanilid and phenacetin will give the "isonitril reaction." C. Platt[e] says:

> Another test useful also in detecting small quantities of acetanilid in the presence of phenacetin is to treat the mixture with caustic soda or potash in the presence of chloroform, when, if acetanilid be present, the characteristic odor of isonitril is given off. If phenacetin be heated with alcohol and sulphuric acid the characteristic odor of ethyl acetate is observed; by heating the solution thus formed with caustic potash and chloroform, the carbylamine reaction is obtained.

In an article entitled "Adulteration and Substitution of Drugs," by Schweitzer,[f] the following statements are found:

> Acetanilid is identified * * * by heating 0.10 gram of the powder with 1 cc of NaOH (15 per cent NaOH) and three drops of chloroform, whereupon the offensive smell of phenyl-isocyanide is given off. * * * For the identification of the mixture (acetanilid and phenacetin) it is sufficient to state that the substance begins to melt at 92° C. and becomes completely transparent below 134° C. On heating 0.10 gram of powder with 1 cc of caustic soda (15 per cent NaOH) and 3 drops of chloroform the offensive smell of phenyl-isocyanide is observed.

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[a] Apoth. Ztg., 1887, **2**: 436, through J. Soc. Chem. Ind., **7**: 227.
[b] Ann. (Liebig), 1899, **309**: 233.
[c] Pharm. Ztg., 1888, **33**: 357.
[d] Ztschr. anal. Chem., **27**: 665.
[e] J. Anal. Appl. Chem., 1893, **7**: 77.
[f] J. Soc. Chem. Ind., 1895, **14**: 852.

According to G. Guasti[a] phenacetin gives the phenyl-carbylamin reaction. F. S. Hyde[b] says: "Contrary to some writers, phenacetin will give the isonitrile test, and hence can not be distinguished from acetanilid by this reaction." F. X. Moerk[c] obtained this reaction in the usual way with both acetanilid and phenacetin, but says that 1 per cent of the former is readily detected in the latter when a solution of potassium permanganate is added to destroy odors that are formed by other bodies and which interfere with the test. P. W. Squire[d] reports satisfactory results with this modification.

The isonitril reaction is recognized as an identifying test for acetanilid by the present British, German, and United States pharmacopœias. Neither of the two former pharmacopœias mentions this test in connection with phenacetin, and the latter does not recognize this chemical. Such careful workers as Helbing, Fischer, and Flückiger state that phenacetin gives the isonitril reaction.

From this array of contradictory statements it is not surprising that a worker not thoroughly familiar with the literature of this subject should make the error of basing his conclusions on this reaction. These discrepancies are undoubtedly due to the fact that phenacetin is less readily decomposed with a fixed alkali solution than is acetanilid. The conditions under which the test has been applied by the various workers have not been uniform, and indeed it would be difficult to prescribe proper limitations, as has been discovered in the drug laboratory. The test has proved itself to be unreliable for the purpose of detecting acetanilid in phenacetin.

COMMERCIAL SAMPLES.

VARIOUS LABELS.

Original 1-ounce packages of the authorized phenacetin were purchased in Washington, D. C., while the unauthorized product and p-acetphenetidin were secured in Philadelphia, Pa. This is not intended to imply that the druggists of Philadelphia were trafficking in the forbidden phenacetin while those in Washington were not.

All samples of the regular article were marked as follows:

Trade-marked name: Phenacetin. Registered trade-mark, 1 Ounce Phenacetin-Bayer. Patented March 26, 1889, U. S. Patent Nr. 400086. Manufactured by Farbenfabriken, vorm. Frieds. Bayer and Co., Elberfeld, Germany, for United States patentee. This package is sold to the owner of U. S. Patent Nr. 400086 March 26, 1889, the Farbenfabriken of Elberfeld Co., 40 Stone Str., New York City.

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[a] Selmi, 1894, **4**: 96, through J. Soc. Chem. Ind., **14**: 77.
[b] J. Amer. Chem. Soc., 1895, **17**: 933.
[c] Am. J. Pharm., 1896, **68**: 89.
[d] Squire's Companion Brit. Pharm., 1899, 17th ed., p. 6.

A general registered trade-mark, No. 31422, consisting of the figure of a winged lion resting one forepaw on a globe while the other paw grasps a caduceus, is also found on each package.

The cartons of the irregular product are plainly marked as to the manufacturer and source of production. Each package is labeled in English, French, and German as follows:

"Patented in the United States of America, Nr. 400086. Phenacetine-Bayer. The resale and importation to the United States of America are prohibited."

The sample purchased by its chemical name bore the following label:

"1 lb. Paracetphenetidine Powder B. P. This serves to remind that this article must not be sold to the United States, it being patented in that country. Made in Germany. E. Merck. Darmstadt."

ANALYTICAL RESULTS.

The tests applied to these samples were such as have been found of service in establishing the quality of phenacetin, and include physical appearance, melting point, solubility, and the presence of p-phenetidin.

Analyses of commercial samples of phenacetin.

Number on package.	Kind.	Physical appearance.	Melting point.	Solubility.	P-phenetidin.
			°C.		
1726	Authorized	Micaceous scales	134.8	Normal.	None.
1743	do	do	135.0	do	Do.
1782	do	do	135.0	do	Do.
04082	Paracetphenidin	Micaceous scales (powdered)	134.9	do	Do.
155641	Unauthorized	Micaceous scales	134.6	do	Do.
339232	Authorized	do	135.0	do	Do.
339243	do	do	134.4	do	Do.
339255	do	do	134.6	do	Do.
845388	Unauthorized	Micaceous scales (some large)	[a]122–123	do	Do.

[a] Began to soften at 94° C.

All of these samples are of satisfactory quality except No. 845388, which is a mixture of phenacetin and acetanilid, containing about 20 per cent of the latter. This sample and the paracetphenidin were purchased at the same place, while the other unauthorized sample was obtained from a different source of supply. On examining the carton containing the mixture of phenacetin and acetanilid it appeared to be spurious. The two empty cartons containing the unauthorized phenacetin were sent to the patentee's agent in New York with the request that he express an opinion as to their genuineness. These packages were immediately returned, No. 845388 being marked counterfeit, the other genuine. The bogus carton resembled the genuine one very closely, though there was a difference in color, style of type, and the ornamental lines employed.

COMMERCE IN PHENACETIN.

United States letters patent grant to an inventor "the exclusive right to make, use, and vend" his "invention throughout the United States and the Territories thereof." This clause effectively restricts to the inventor, his heirs, or assignees, the right to import his patented product into the United States when manufactured abroad. According to certain decisions[a] it is held by some that if the article is purchased from the patentees, tribute has been paid to the monopoly and the right is therefore acquired to import, use, and sell the article, bought elsewhere, within the United States. This privilege, however, does not obtain when purchases are made from others than the owners of the patent, because they have not then received any remuneration for the article so purchased.[b] If these principles governed the phenacetin trade the present strained situation would not exist.

Another factor which has assumed considerable proportions in the commercial world must be considered. The patentee has the right and power to sell his product subject to the express conditions that it must not be imported into the United States or sold here. He has the same vested right to sell the product with restrictions and limitations that he has to sell it at all. It is a matter of record that the patentees of phenacetin expressly state on every package sold in foreign countries that its importation into the United States and resale there is prohibited. Manufacturers of p-acetphenetidin specify on every package that it must not be sold in the United States. The following extracts from the decisions of the United States circuit court of appeals[c] express the rulings on this point in a very succinct manner:

1. One purchasing in a foreign country an article protected by a United States patent, from persons other than the owner of the United States patent or his vendees, can not import and sell the same in this country without infringing the United States patent.

2. One purchasing in a foreign country, from the owner of the United States patent, patented goods having marked upon them a condition that they should not be imported into the United States, can not import and sell them here without being guilty of infringement.

Judging from past reports and recent developments, our excise laws have been grossly violated by the smuggling of phenacetin, which is clandestinely brought into the country in violation of our customs laws, or is regularly imported, duty paid, and secretly sold to consumers. Pharmaceutical journals recount the arrests of numerous vendors of this illicit product. These smugglers have been apprehended in every section of the Union, and many litigations have been instituted, numerous injunctions issued, and fines imposed.

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[a] Cited in Dickerson *v.* Tinling, Fed. Rept., 1898, **84**: 192.
[b] Dickerson *v.* Tinling, Fed. Rept., 1898, **84**: 192.
[c] Dickerson *v.* Tinling, Fed. Rept., 1897, **84**: 192.

The collector of customs of the port of New York seized and confiscated illegally imported phenacetin, advertised it for sale in the customary manner, and sold it at public auction in that city in 1898. The purchaser at the time of the sale knew that the goods were smuggled, and infringed the patent. Before he could resell his purchase the representative of the patentees served an injunction preventing such sale. The case was taken into the United States circuit court, and the defendant enjoined from directly or indirectly using or selling the patented drug phenacetin. An appeal was taken to the United States circuit court of appeals, and this court affirmed the order of the lower court.[a] The defendant claimed, first, that the passage of the phenacetin through the hands of the Federal Government in some way abrogated the rights of the patentee; and, second, that by the condemnation proceedings and statutory notice the title of the property passed to the purchaser without incumbrance or reservation.

In view of the decision given above, it seems that these contentions do not obtain in the case of patented articles of the phenacetin type. The decision further states that the patentee "has no title to or lien on, or legal or equitable interest in the infringing property." The purchaser filed an application for a refund of the buying price, but the Treasury Department reported that it could not comply with this request,[b] as the law does not provide for refunds under any circumstances. The defendant refused to comply with the order to surrender the goods purchased from the Government. This curious legal entanglement as to the disposition of smuggled patented drugs is at present receiving the consideration of the Attorney-General. The issue is of the greatest importance, and has attracted the attention not only of the Treasury officials, but of the Patent Office authorities as well.

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[a] Dickerson *v.* Sheldon, Fed. Rept., 1900, 98: 621.

[b] Oil, Paint, and Drug Reporter, August, 1903, 64: 24.

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